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Review Article

Neuronal Hyperexcitability: The Elusive But Modifiable Instigator of Disease

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Abstract: Despite enormous strides in medical diagnostics and the ability to analyze and track disease processes, the underlying cause of most psychiatric and medical disorders remains unclear. Consequently, the treatment of these disorders continues to be more palliative than preventive. However, an emerging hypothesis contends that severe and persistent stress is at the root of most psychiatric and general medical conditions. Although this idea is not new, what is new is the identification of a powerful but elusive endogenous driver of the stress. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) hypothesis, ordinary daily stressors are abnormally amplified by an inherent hyperexcitability of the neurological system. This pathophysiological trait, which appears to be inherited in an autosomal dominant distribution and expressed through the central and peripheral nervous systems, causes shockwaves to be repeatedly sent through the body, keeping it in fight-or-flight mode much or all of the time. The strain that this commonly-occurring trait places on various organs and systems of the body can cause repeated bouts of mental illness and a gradual progression of physical illnesses such as diabetes mellitus, high blood pressure, cardiovascular disease, autoimmune diseases, cancer, and dementia. Although the etiology of most illnesses is thought to be multifactorial, the genealogical distribution in which they occur and the relationship that they have to one another strongly suggests that among the various psychological, biological, and environmental factors that contribute to their development, the trait of neuronal hyperexcitability is the most important. This observation has enormous implications because neuronal hyperexcitability is a highly modifiable risk factor. Any psychological, behavioral, dietary, or medical intervention that quiets the nervous system can potentially prevent or delay the development of the various illnesses that are thought to be fueled by the neuronal hyperexcitability trait. In addition, there is emerging evidence that the trait can be detected through resting vital-sign measurements. The ease of this objective measurement and the power that it has to incentivize affected persons to take control of their health underscores the importance of recognizing the connection between neuronal hyperexcitability and the pathogenesis of disease.

Keywords: Neuronal Hyperexcitability, Biomarkers of Disease, Preventive Medicine, Anticonvulsants, Pathophysiology of Psychiatric Disorders, Genetics of Psychiatric Disorders

1. Introduction

Despite the enormous strides that have been made in medical diagnostics and the ability to analyze and track disease processes, the underlying cause of most psychiatric and medical disorders remains unclear. Consequently, the treatment of these disorders continues to be more palliative than preventive. However, an emerging hypothesis contends that severe and persistent stress is at the root of most psychiatric and general medical conditions [1, 2]. Although the idea that stress can precipitate or exacerbate illness is not new, what is new is the identification of a powerful but elusive endogenous driver of the stress. According to the Multi-Circuit Neuronal Hyperexcitability (MCNH) hypothesis, every life stressor, whether it be psychological, emotional, or biological, is abnormally amplified by an inherent hyperexcitability of the neurological system [1]. This commonly-occurring pathophysiological trait, which expresses itself through the central and peripheral nervous

systems, sends continual shockwaves through the body, keeping it in fight-or-flight mode much or all of the time [1]. Because the cognitive-emotional system is exquisitely sensitive to neuronal excitation, psychiatric symptoms are typically the first manifestations of the trait [1]. Other early manifestations of the trait are the various "functional" physical symptoms that are commonly associated with psychiatric disorders, such as migraine headaches, irritable bowel, fibromyalgia, and other physical symptoms that have no demonstrable organic etiology [1]. Though all of the aforementioned symptoms are reversible, the underlying abnormality also tends, over time, to have a progressive erosive effect on various organs and systems of the body, thus helping to explain the link between mental illness and the early onset of various disease processes, such as diabetes, high blood pressure, cardiovascular disease, autoimmune disease, cancer, and dementia [1, 2]. This article will discuss the mechanisms by which these deleterious effects occur and the importance of identifying and attenuating the neuronal hyperexcitability trait as early in life as possible.

2. Pathological Effects of the Neuronal Hyperexcitability Trait

2.1. Early Manifestations

2.1.1. Psychiatric Manifestations

Because the nervous system regulates virtually every mental, emotional, and physical function of the body, neuronal hyperexcitability, which describes a physiological aberration in this system, affects virtually every process in the body. The first and most obvious of these is cognitive-emotional processing. Because thoughts and emotions are exquisitely sensitive to neuronal excitation, a hyperexcitability of the neurons and circuits to which specific thoughts and emotions are linked would cause them to be abnormally intense and persistent [1, 3, 4]. This effect, which is the basis of the MCNH Hypothesis of Psychiatric Disorders, is what makes psychiatric symptomatology the first subjective marker of the neuronal hyperexcitability trait. Some of the most common psychiatric manifestations of neuronal hyperexcitability are persistent feelings of anxiety, persistent feelings of depression, persistent feelings of anger, and persistent feelings of euphoria. What causes these and other emotions to be abnormally intense and abnormally prolonged is the inability of the associated neurons to self-regulate. Other common manifestations of neuronal hyperexcitability include racing thoughts, which are thought to be driven by aberrant discharges in the brain similar to ectopic beats of the heart; obsessive thoughts, which are thought to be driven by a failure of specific neurons and circuits to shut off despite mental efforts to shift thinking; compulsive behaviors, which are thought to be driven by efforts to reduce the anxiety associated with persistent hyperactivity in symptom-related cognitive-emotional circuits; hyper-emotionality, which is thought to be driven by hyperactivity in limbic circuitry; hyper-reactivity, which is thought to be driven by a hyper-responsiveness of hyperexcitable neurons; sensory hypersensitivity, which is thought to be driven by an abnormal amplification of sensory input; inattention, which is thought to be driven by an overabundance of neural signaling; impulsivity, which is thought to be driven by an inability of the brain to fully think things through in conjunction with the mind before a distracting thought is stimulated by the hyperactive brain; physical hyperactivity, which is thought to be driven by a hyperactivity of the associated neurons and circuits; pressured speech, which is thought to be driven by cognitive and emotional flooding; symptom-cycling, which is thought to be driven by a migration of the locus of hyperactivity to inappropriate cognitive-emotional circuits; insomnia, which is thought to be driven by a resistance of hyperactive circuits to appropriately respond to normal sleep-wake mechanisms; psychotic symptoms, which are thought to develop when the electrical activity in the sensory processing system becomes as high as the activity that would normally be driven by external stimuli; and substance misuse, which is thought to represent desperate attempts to control the extreme and unpredictable changes in emotion that are driven by neuronal hyperexcitability.

Although all of these psychiatric symptoms can theoretically be driven by stress alone, the level of stress would have to be unusually high for an extended period of time to induce enough kindling to precipitate them in the absence of neuronal hyperexcitability. First observed by Graham Goddard in his experiments on rats [5], kindling describes the natural tendency for neurons to become increasingly responsive with repeated stimulation. This adaptive process, which under normal physiological conditions is more aptly described as "primed burst potentiation" [6], is the MCNH explanation for why the onset of psychiatric symptoms tends to be delayed relative to the onset of a triggering stressor.

Perhaps because environmental stressors can have the same effect as neuronal hyperexcitability, and because the neuronal hyperexcitability trait does not become clinically apparent until the hyperexcitable brain, like a hive of temperamental bees, becomes perturbed by an environmental stressor, the significance of the neuronal hyperexcitability trait has heretofore gone largely unrecognized.

2.1.2. Functional Physical Manifestations

Just as neuronal hyperexcitability can abnormally amplify thoughts and emotions, it can abnormally amplify electrical signals to and from specific organs and tissues. In the process, these body parts can become symptomatic even in the absence of any physical abnormality. However, the nature of the symptoms, being physical, again makes it easy to overlook the possibility that they could be driven by a neurophysiological abnormality [1, 3].

Another common way that the neuronal hyperexcitability trait could express itself early in life is in the body's response to infection. When the neurological system is hyperexcitable, immunological responses tend to be dysregulated [7]. Although it had long been thought that neurological function

and immunological function were largely independent of each other, a growing body of literature suggests that the nervous system can influence the immunological system through both neural and non-neural pathways [8, 9]. For example, the amygdala, through its inputs to the both the locus coeruleus and the hypothalamic-pituitary axis, can, either directly or indirectly, stimulate the release of adrenaline, cortisol, and other mediators of inflammation [9, 10]. There is clinical and experimental evidence that these mediators both activate and dysregulate the immunological system [9, 10]. Acute short-term stress, such as taking an exam, tends to impair cellular immunity, whilst chronic stress tends to impair both cellular and humoral immunity [10]. At the same time, the associated increase in cytokine production increases the excitability of the neurological system [11], thereby creating a vicious cycle of mutual overstimulation between the neurological and immunological systems [12]. The resulting hyperinflammatory state increases the risk of environmental allergies [9] and, in some cases, causes healthy tissue to be attacked, thus resulting in autoimmune diseases [12]. This is the MCNH explanation for the link between psychiatric disorders and these disease processes. It also helps explain why persons with a psychiatric history tend to have more complicated recoveries from viral and bacterial infections [13]. The risk of these complications is further increased by stress, thus explaining the temporal link between stress and the onset of environmental allergies, autoimmune diseases, and infectious diseases [9, 10, 12].

2.2. Later Manifestations

Unlike the early manifestations of neuronal hyperexcitability, many of which are reversible, the later manifestations tend to be more permanent because they express the gradual erosive effects of the neuronal hyperexcitability trait [1, 2]. Some examples of these include atherosclerosis, high blood pressure, heart disease, chronic musculoskeletal pain, osteoarthritis, malignancies, and dementia [1, 2]. Although these diseases can potentially occur in anyone, the risk of developing them tends to be increased and their progression tends to be accelerated when the neurological system is hyperexcitable. Both physiologically and heuristically this makes sense, for just as neuronal hyperexcitability tends to disrupt the cognitive-emotional system, it can disrupt the muscular system, the endocrine system, the metabolic system, the cardiovascular system, and the cerebrovascular system [1].

For example, a hyperexcitability of the neurological system tends to drive a subtle elevation in resting muscle tension together with an abnormal elevation in muscular responsiveness to emotional and physical stressors [1]. Although this may not be very noticeable early in life or when stress levels are low, repeated bouts of high stress consequent to the superimposition of normal life stressors upon an inherent hyperexcitability of the neurological system can hasten the development of hypertonic spasm, a permanent and more severe state of muscle hypertonicity that has been hypothesized to be the root cause of chronic musculoskeletal pain [14]. In addition to the irritating effect that hypertonic muscle can have on local nerves, the sensory signals that are relayed by those nerves to the spinal cord tend to be abnormally amplified, as does the higher processing of those signals by the brain. This is the MCNH explanation for the link between psychiatric disorders and chronic pain disorders such as sciatica, fibromyalgia, and some neuropathies.

As another example, recurrent stressors superimposed upon a hyperexcitability of the neurological system can drive a hyperinflammatory state and recurrent cyctokine storms, which, over time, can have a deleterious effect on multiple organs and tissues.

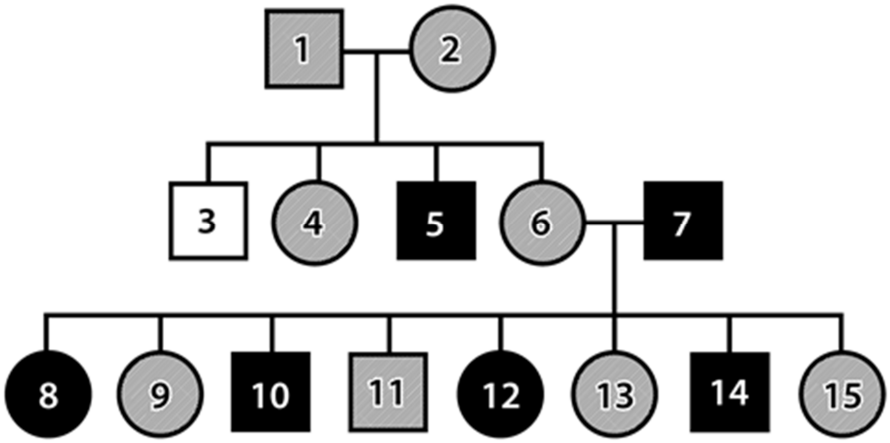
As previously mentioned, other systems of the body that can become dysregulated by a hyperexcitability of the neurological system include the metabolic, the cardiovascular, and the endocrine systems. An exploding body of literature describes how a dysregulation of these interacting systems can lead to a cluster of physiological abnormalities that include insulin resistance, obesity, hypertension, and dyslipidemia. Although the pathophysiology of these commonly-occurring abnormalities, known as “metabolic syndrome,” has been extensively described [15-17], the cause of them has yet to be fully elucidated. Undoubtedly, stress and an unhealthy lifestyle are important contributors, but these factors alone would not explain why some persons are more vulnerable to developing metabolic syndrome than others. What makes neuronal hyperexcitability even more germane to the discussion is that all of the psychosocial and behavioral contributors to metabolic syndrome, including poor dietary choices, physical inactivity, poor sleep, and substance misuse, are themselves driven by neuronal hyperexcitability [1].

That raises the question of how influential the trait of neuronal hyperexcitability is in comparison to other contributors to disease formation and progression.

3. Clinical Significance of the Neuronal Hyperexcitability Trait

The answer to the question of clinical significance lies in the familial distribution of the aforementioned psychiatric and medical abnormalities. Although extensive data from family, twin, and adoption studies indicate that psychiatric disorders and their common comorbidities have a significant genetic component, individual disorders fail to show a consistent pattern of inheritance. However, if one considers the varying degrees to which the neuronal hyperexcitability trait can be expressed and the diversity of forms that its expression can take, one could not reasonably expect the same symptomatology to be passed from one generation to the next even if the same gene variants were inherited. If, with this in mind, we go back and reconstruct family pedigrees based not on specific constellations of symptoms but on overt as well as soft signs of neuronal hyperexcitability, such as hyperemotionality, mood instability, sleep abnormalities, attentional problems, functional somatic symptoms, and substance use disorders, a consistent pattern of distribution

emerges; that pattern is strikingly autosomal dominant! (Figure 1). The validity of this observation is supported by the additional observation that a predictable proportion of children in these families seem to be resistant to developing psychiatric symptoms irrespective of how dysfunctional their family dynamics might be (Figure 1). These so-called "survivors," who appear in a classic autosomal recessive distribution, are not necessarily more mentally tough than their siblings but rather more neurologically stable presumably because they did not inherit one of the gene variants that have been linked to neuronal hyperexcitability. Moreover, the fact that these individuals are also relatively resistant to physical illness suggests that among the variables that contribute to the development of disease, the trait of neuronal hyperexcitability is the most important. Note that some of the children (black symbols) have more significant disease than others (shaded symbols). The noticeable difference in phenotypic expression suggests that the trait of neuronal hyperexcitability is also additive. The autosomal dominant pattern of inheritance, the additive nature of the trait, and the sharp clinical distinction between those who hypothetically inherent the gene polymorphisms for neuronal hyperexcitability and those who do not suggest that most of the candidate genes that have been linked to chronic mental and physical illnesses make small contributions in comparison to a few genes that make large contributions and may by themselves be enough to markedly increase one's vulnerability to developing a chronic illness.



WHITE: Normal
SHADED: Heterozygous Carrier (mild-moderate neuronal hyperexcitability)
BLACK: Homozygous Carrier (severe neuronal hyperexcitability)

HR: Heart Rate
RR: Respiratory Rate

1. Generalized anxiety disorder (HR=75; RR=17)
2. Persistent depressive disorder; Eating disorder (HR=82; RR=18)
3. Normal (HR=63; RR=11)
4. Mild obsessive-compulsive disorder; Eczema (HR=75; RR=16)
5. Schizoaffective disorder; Panic disorder; Obesity; Cardiovascular disease (HR=79; RR=23)
6. Fibromyalgia; Hypothyroidism (HR=70; RR=24)
7. Cyclothymic disorder; Panic disorder; Crohn's disease (HR=83; RR=14)
8. Borderline personality disorder; Migraine; Hypertension; Chronic pancreatitis (HR=86; RR=20)
9. Persistent depressive disorder; Irritable bowel syndrome (HR=79; RR=17)
10. Bipolar I disorder; ADHD; Alcohol use disorder; Hypertension; Cardiovascular disease; Obesity; Alzheimer's disease (HR=87; RR=22)
11. Generalized anxiety disorder; Body dysmorphic disorder (HR=75; RR=18)
12. Panic disorder; Histrionic personality disorder; ADHD (HR=80; RR=22)
13. Persistent depressive disorder; Tension headaches (HR=77; RR=17)
14. Post-traumatic stress disorder; Panic disorder; Schizotypal personality disorder; Cardiovascular disease (HR=87; RR=19)
15. Hyperthymic temperament; ADHD; hypothyroidism (HR=80; RR=16)

Figure 1. *Representative family pedigree illustrating the autosomal dominant inheritance pattern of the neuronal hyperexcitability trait. Also listed are the associated resting vital-sign measurements. Illustration is based on more than 300 consecutive clinical interviews.*

4. Practical Benefits of Identifying the Neuronal Hyperexcitability Trait

What this implies is that de-stressing the neurological system could have a substantial protective effect against developing any of a wide range of mental and physical conditions. This could help explain why healthy lifestyle habits, such as judicious time management, proper rest, regular exercise, avoidance of caffeine, and minimization of refined sugar, have traditionally been so helpful in preventing and even reversing many disease processes. Even so, the powerful negative influence that the trait of neuronal hyperexcitability confers on motivation and behavior could prevent even the most well-intended persons from establishing and maintaining the aforementioned habits and routines. Furthermore, the effectiveness of natural interventions is limited by the fact that they do not correct the gene abnormality that is believed to underlie the neuronal hyperexcitability trait [3]. Consequently, for persons with higher levels of neuronal hyperexcitability, natural interventions may neither be practically doable nor biologically sufficient to prevent the consequences of neuronal hyperexcitability [1, 3]. Such persons may require additional education about their condition together with effective brain-calming medications. The advantage of medication, even without the adoption of healthy lifestyle habits, is that it generally provides more improvement than lifestyle changes and, through that improvement, allows a person to successfully make healthy lifestyle changes.

Then again, this approach is, like most medical approaches, primarily reactive: symptoms develop, and treatment is applied. What is unique about the MCNH hypothesis is that it also guides the use of anticonvulsants, which could more aptly be called "Neuroregulators" because of their putative mechanism of action, as a prophylactic intervention. That is to say, if the trait of neuronal hyperexcitability could be detected before life stressors had a chance to create enough kindling to precipitate symptoms, treatment with Neuroregulators could prevent psychiatric symptoms from ever developing. They could also prevent the more subtle but more pernicious consequences of neuronal hyperexcitability, such as low self-esteem, unhealthy peer relations, academic difficulties, risk-taking behavior, eating disorders, and substance misuse. Early treatment with Neuroregulators could possibly also prevent the development any of a number of early-onset physical conditions, such as adolescent obesity, essential hypertension, diabetes type-1, and autoimmune diseases [2]. Although such an early use of medication might sound overly aggressive, the prophylactic use of Neuroregulators, like the help of a little rain in preventing a forrest fire, could have subtle but profoundly protective effects [18]. These effects could also help prevent the more delayed but more enduring consequences of neuronal hyperexcitability, such as high blood pressure, cardiovascular disease, hypothyroidism, arthritis, chronic musculoskeletal pain, cancer, and dementia.

The trait of neuronal hyperexcitability, like near-sightedness, is estimated to affect nearly one-half of the world's population [19]. Without early detection and treatment, the healthcare crisis will continue to escalate, as most affected children will develop attitudes and behaviors that take them further and further off course in life. That underscores the importance of identifying the neuronal hyperexcitability trait as early as possible.

5. How to Identify the Trait Before Symptoms Begin

In the past, identifying the trait of neuronal hyperexcitability would have depended upon a physician's clinical assessment and inquiries about a patient's behavior, lifestyle, and relationships. Fortuitously, however, there is growing evidence that the trait can be detected by simply measuring one's resting vital signs [1]. For example, in a longitudinal study involving more than 1 million men in Sweden, Latvala et al. [20] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [21] found that adolescent girls with emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of physical illnesses, including diabetes, high blood pressure, cardiovascular disease, autoimmune diseases, and all-cause mortality [1]. Based on these studies, which are rapidly accumulating, it has been estimated that an RHR above 75 beats/min or an RRR above 15 breaths/min is indicative of the neuronal hyperexcitability trait [1]. Note, however, that these vital-sign elevations, which are thought to be the consequence of a tonic elevation in basal neurological activity in carriers of the alleles for neuronal hyperexcitability [1], are not necessarily outside the accepted range of "normal" but rather on the upper end of normal (Figure 1) [1]. In an era of smartphones, wearable devices, and a growing public desire to prevent rather than chase after illness, an objective method of identifying the neuronal hyperexcitability trait could usher in history's greatest campaign in the fight against sickness and disease.

6. Discussion

Despite an explosion of medical technology and sophisticated new treatments, the underlying cause of most mental and physical disorders remains poorly understood. Getting to the root of these disorders is of paramount importance because it could reveal a modifiable risk factor and, thus, help reduce the incidence and severity of disease.

In an effort to solve the mystery of mental illness, it was found not only that nearly all psychiatric disorders were rooted in a shared physiological abnormality but also that nearly all degenerative medical conditions are rooted in the

same physiological abnormality. That abnormality is an inherent hyperexcitability of the neurological system. Simply put, neuronal hyperexcitability amplifies the stress response, thus accelerating the onset and progression of any disorder that can be precipitated or exacerbated by stress.

Although a diversity of environmental factors and numerous candidate genes have been linked to various disease processes, the apparent autosomal dominant distribution of the neuronal hyperexcitability trait and the tendency for a variety of psychiatric, functional, and general medical conditions to follow the same distribution suggests not only that neuronal hyperexcitability is at the root of most psychiatric and chronic medical conditions but also that the trait prevails over other contributing factors in its degree of influence.

This has enormous implications for several reasons. First, it identifies a highly modifiable, easy-to-identify source of vulnerability for a wide range of psychiatric and general medication conditions. Second, it provides a clear biological target for the treatment of psychiatric disorders, an advance that has eluded the medical field since antiquity. Third, by showing that mental illness and physical illness have a common root, it helps reduce the stigma of mental illness. Fourth, it unites natural preventive measures, such as diet, exercise, and stress-reduction, with relatively safe pharmacological interventions (i.e., anticonvulsant drugs) in the fight to prevent sickness and disease. Fifth, it provides a simple, objective means by which patients can identify their own vulnerability to illness and, thus, take control of their health. Sixth, it can reduce the cost of healthcare by streamlining treatment and opening the door to a whole new world of prevention. Seventh, it carries the potential to curtail discriminatory practices that limit insurance coverage for mental health services.

Although several new theories of psychopathology have been proposed in recent years, such as the immune, the endocrine, the glutamatergic, the GABAergic, the mitochondrial, and the neuroplastic, these theories, like the theories of most disease processes, describe pathological processes but fail to identify what makes one vulnerable to those processes. Even when a disease process is thought to be genetically-based, the means by which the gene abnormally leads to disease is seldom specified. In the case of neuronal hyperexcitability, however, both the gene abnormality and the means by which it leads to disease are identified. In addition, an easily-measurable, objective means of detecting the abnormally and multiple means of therapeutically modifying the abnormality are identified. This is groundbreaking because the underlying abnormality is hypothesized to be the primary cause of most mental and physical illnesses.

Urgently needed are clinical studies aimed at assessing 1) the accuracy of resting vital signs in predicting the development of various psychiatric and substance use disorders; 2) the effectiveness of using Neuroregulators prophylactically in teens with upper-end-of-normal resting vital signs; 3) the effectiveness of using Neuroregulators long-term to prevent the development of various psychiatric and medical conditions; 4) the relationship between resting vital-sign measurements and variants of the risk genes for neuronal hyperexcitability; and 5) the effectiveness of prophylactic Neuroregulator therapy in teens who test positive for variants of the risk genes for neuronal hyperexcitability.

7. Conclusion

In identifying the core vulnerability trait in most psychiatric and medical illnesses, the MCNH hypothesis informs a corrective measure that integrates natural interventions, such as stress-reduction, diet, and exercise, with well-tested, inexpensive pharmacotherapies to both reduce the risk of disease and help alleviate acute symptoms. In so-doing, it also reduces the need to distinguish mental disorders from physical disorders or even one mental disorder from another.

Although the MCNH hypothesis has yet to be verified through rigorous scientific studies, the logic, simplicity, and explanatory power of the hypothesis bear witness to its validity. Many of the greatest scientists and thinkers throughout history have said that the beauty and simplicity of a theory is greater evidence of truth than scientific experimentation. “Beauty brings with itself evidence that enlightens without mediation,” wrote Hans Von Balthasar, one of history’s most renowned philosophers. By opening the door to powerful and easy-to-implement preventive strategies, the MCNH hypothesis could be ushering in a paradigm shift in public health that would, to an unprecedented degree, reduce the burden of mental illness, curb the risk of major medical illnesses, and slash healthcare costs.

Disclosure Statement

The author declares that this article was conceived and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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